Bergamot Polyphenols Protect Against Doxorubicin-Induced Cardiomyopathy Reducing ROS Production And Promoting Myocyte Survival

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Doxorubicin (DOXO) is one of the most widely used antineoplastic drugs. Despite its highly beneficial effects against several neoplasias, the clinical use of DOXO has the serious drawback of cardiotoxicity, which over time causes a cardiomyopathy that leads to congestive heart failure. The molecular pathogenesis of anthracycline cardiotoxicity remains highly controversial, although the oxidative stress-based hypothesis involving intramyocardial production of reactive oxygen species (ROS) has obtained great interest.

In this regard, dietary polyphenols, in particular flavonoids, play a cardiovascular protecting role due to their pleiotropic anti-oxidative and anti-inflammatory effects. Thus, we have investigated whether a rich mixture of flavonoids extracted from Bergamot (*Citrus Bergamia Risso et Poiteau)*, the bergamot-derived polyphenolic fraction (BPF), could attenuate DOXO-induced cardiomyopathy *in vivo*.

Here we show that BPF was able to prevent DOXO-induced cardiac tissue strain dysfunction and as a consequent left ventricular (LV) cardiac impairment. Indeed, echocardiographic assessment demonstrated that BPF administration in DOXO+BPF group significantly reduced LV end-systolic diameter (LVES*d*), LV end-diastolic diameter (LVED*d*), inter-ventricular septum in systole and diastole (IVS*s* and IVS*d*), left ventricular posterior wall in systole and diastole (LVPW*s* ad LVPW*d*), LV systolic and diastolic volume (LV-Vol*s* and LV-Vol*d*), improving both ejection fraction (EF) and fractional shortening (FS) when compared to DOXO-treated rats.

Moreover, BPF was able to prevent time-to-Peak (TPk) delay of cardiac strain and strain rate and dyssynchrony of radial motion in short axis when compared to DOXO group.

Histological analysis of DOXO+BPF-treated rats revealed a significant reduction of myocyte apoptosis, accompanied by a decrease in reactive myocyte hypertrophy and myocardial fibrosis when compared to DOXO-treated rats.

BPF was able to significantly counteracts the increase in lipid peroxidation and tyrosine nitration of cardiomyocytes isolated from DOXO-treated rats.

In conclusion, bergamot-derived polyphenols reduce DOXO-induced cardiotoxicity decreasing ROS production and myocyte apoptosis that leads to a significant improvement of cardiac function. These data suggest that a BPF may be used as a promising cardioprotective agent in patients requiring anthracycline chemotherapy. So further clinical trials are required to confirm those findings.